REMARKS

Claims 1, 2, 6, and 10 are amended. New Claims 16, 17 and 18 have been added. Support for the amendments and the new claims can be found in the Specification as filed, for example, in Figure 1 and on page 9, line 3 - page 11, line 4. The following addresses the substance of the Final Office Action.

Claim rejections under 35 USC §112

The Examiner has rejected claims 1, 4, 6, 7, 10, 14 and 15 under 35 USC §112, first paragraph as not enabled.

The Examiner acknowledged that the Specification as filed is enabling for a genetically modified female mouse, whose genome comprises a homozygous mutation, a partially homozygous deletion or a totally homozygous deletion in the endogenous genetic sequence encoding the wild-type aplha-fetoprotein (AFP), wherein said mouse does not express a functionally active AFP, is sterile, and does not undergo a complete oestrous cycle. The Examiner also acknowledged that the Specification as filed is enabling for a method of identifying a candidate agent for use in treating osteoporosis, infertility, or preventing conception which comprises utilizing the above-described genetically-modified female mouse.

The Examiner asserts that the specification does not enable a sterile female genetically modified mouse, wherein the mutated, deleted, or partially deleted AFP could still be expressed, and/or wherein only a heterozygous mutation, partial deletion, or a total deletion in one of the alleles, which contains the endogenous genetic sequence encoding the AFP.

Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986). "To be enabling, the specification of a patent must teach those skilled in the art to make and use the full scope of the claimed invention without 'undue experimentation' ... Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples." *See In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993).

With respect to sterile female genetically modified mice, wherein the mutated, deleted, or partially deleted AFP could still be expressed, Applicants note that as attested in the accompanying Declaration, as of the priority date of the present application (July 12, 1999) a variety of targeted techniques for modifying the mouse genome were known to those skilled in

the art. In addition, the sequence of the mouse AFP protein was known. In fact, using the techniques known as of the priority date of the present application, one of skill in the art could readily introduce any desired mutation, deletion, or partial deletion into the mouse AFP gene. In addition, since the sequence of the mouse AFP protein and gene were known one of skill in the art could readily design modifications which would prevent the expression of sufficient active AFP protein to confer fertility.

The Specification provides a step-by step description of one way of disrupting an AFP allele by deleting Exons 1-3 of the AFP gene using ES cells (partial deletion of the AFP gene). However, as attested in the accompanying Declaration, other methods of targeted modification of the AFP gene existed at the time this application was filed. The same methodology used to generate the partial deletion can also be used to generate a complete deletion. In addition, as of the priority date of the present application, a skilled artisan following the teaching of the present specification regarding importance of both copies of functional AFP in fertility had a whole array of methods of constructing mutations in the AFP gene which would render female mice sterile, including site-directed point mutations generated by the "tag-and-exchange" method, and "hit-and-run" method. Thus one of skill in the art could readily introduce mutations, such as frameshift mutations, point mutations, or partial deletions which would prevent female mice from producing sufficient active AFP protein to confer fertility.

The Examiner also asserts that Claim 13 is not enabled, because there is no evidence that any useful phenotype can be affected by a heterozygous AFP+/- mouse. Applicants note that Claim 13 is withdrawn and relates to stem cells. Accordingly, Applicants assume that the Examiner was referring to Claim 14, which relates to heterozygous mice.

Applicants maintain that heterozygous AFP+/- mice are useful because they can be used to generate mice which do not express sufficient active AFP to confer fertility. In addition, Applicants note that the Specification demonstrates the generation of mice which are heterozygous for a partial deletion of the AFP gene and the use of such mice to generate sterile female mice. Heterozygous mice carrying one copy of an AFP mutation can then be mated to obtain offspring which have both alleles of the AFP gene modified, causing the females to become sterile. The heterozygous parents which are mated can carry the same or different modification in the AFP gene and the result of their mating will be the same as taught by the present invention: female sterility. Therefore, Applicant asserts that Claims 1, 4, 6, 7, 10, 14, 15,

and new claims 16, 17 and 18 are enabled, and their rejection under 35 USC §112, first paragraph should be withdrawn.

CONCLUSION

Applicants have endeavored to address all of the Examiner's concerns as expressed in the outstanding Office Action. Accordingly, amendments to the claims, the reasons therefor, and arguments in support of the patentability of the pending claim set are presented above. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Feb. 4, 2005

By: Daniel Hart

Daniel Hart
Registration No. 40,637
Attorney of Record
Customer No. 20,995
(619) 235-8550

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